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BRIEF REVIEW ON DIAGNOSTIC TECHNIQUE AND NOVEL MOLECULES IN CLINICAL TRIALS FOR TREATMENT OF BREAST CANCER

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ABSTRACT

Breast cancer is the most common cancer in women in both developed and undeveloped countries, and the second most frequent cause of cancer deaths after lung cancer. Although there have been many chemotherapeutic agents like 5-fluorouracil, taxol, tamoxifen, doxorubicin, cisplatin, and camptothecin and hormones are used to treat breast cancer. This review focuses on the causes of breast cancer, latest diagnostic techniques and various molecules under clinical trials for the treatment of breast cancer.

Key word: Breast cancer, Diagnostic Technique, Novel synthetic molecule.

INTRODUCTION

Breast cancer is a type of cancer originating from breast tissue, most commonly from the inner lining of milk ducts or the lobules that supply the ducts with milk. Breast cancer is a malignant tumor that starts in the cells of the breast [1].

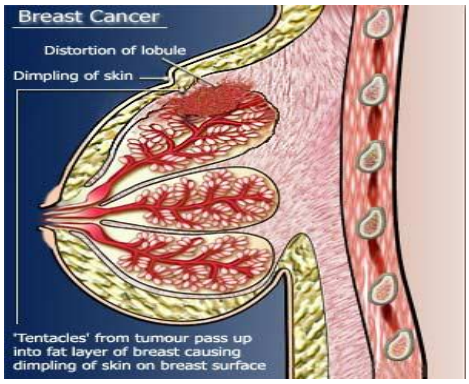


Fig. 1: Breast cancer.

Epidemiology

Worldwide, breast cancer is the most common invasive cancer in women. Breast cancer comprises 22.9% of invasive cancers in women and 16% of all female cancers. In 2012, breast cancer caused 5, 21,000 deaths worldwide [2].

The breast lymphatic system

This system has several parts. Lymph nodes are small, bean-shaped collections of immune system cells that are connected by lymphatic vessels. Lymphatic vessels carry a clear fluid called *lymph* away from the breast. Lymph contains tissue fluid and waste products, as well as immune system cells. Breast cancer cells can enter lymphatic vessels and begin to grow in lymph nodes. Most lymphatic vessels in the breast connect to lymph nodes under the arm some lymphatic vessels connect to lymph nodes inside the chest (internal mammary nodes) and those either above or below the collarbone [3].

Benign breast lumps

Benign breast tumors are non-cancerous areas where breast cells have grown abnormally and rapidly, often forming a lump. Unlike cysts, which are filled with fluid, tumors are solid. Benign breast tumors are not dangerous and do not spread outside the breast to other organs [4].

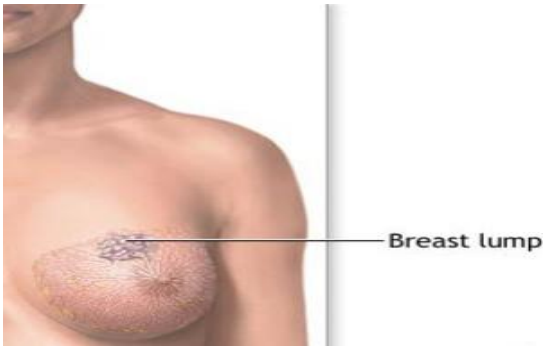


Fig. 2: Benign breast lumps.

Fibrosis and cysts

Most lumps turn out to be caused by fibrosis and/or cysts. Fibrosis is the formation of scar-like (fibrous) tissue, and cysts are fluid-filled sacs [5].

Fibroadenomas and Intraductal Papillomas

Fibroadenomas are benign tumors made up of both glandular breast tissue and connective tissue. The use of birth control pills before age 20 is linked to the risk of fibroadenomas [6, 7].

Two types of intraductal papillomas are generally distinguished. The central type develops near the nipple. They are usually solitary and often arise in the period nearing menopause. On the other hand, the peripheral types are often multiple papillomas arising at the peripheral breasts, and are usually found in younger women.

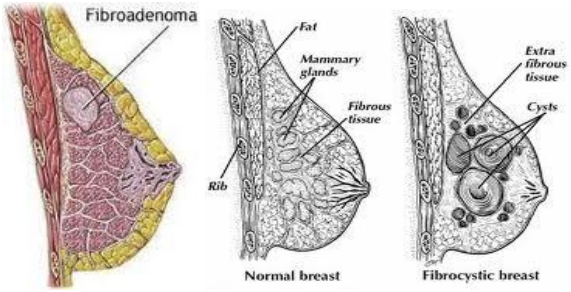


Fig. 3: Fibroadenomas and fibrocystic disease.

Types of breast cancers

Invasive Ductal carcinoma [8]

Invasive ductal carcinoma (IDC), sometimes called infiltrating ductal carcinoma, is the most common type of breast cancer. About 80% of all breast cancers are invasive ductal carcinomas.

On a mammogram, it is usually visualized as a mass with fine spikes radiating from the edges. On physical examination, this lump usually feels much harder or firmer than benign breast lesions such as fibroadenoma. On microscopic examination, the cancerous cells invade and replace the surrounding normal tissues.

The prognosis of IDC depends, in part, on its histological subtype. Mucinous, papillary, cribriform, and tubular carcinomas have longer survival, and lower recurrence rates. Also some rare forms of breast cancer like sarcomatoid and inflammatory carcinoma have a poor prognosis.

Tubular Carcinoma [9]

Tubular carcinoma cells have a distinctive tubular structure when viewed under a microscope. Tubular breast cancer is an invasive type of cancer, which means it has spread from the ducts into the surrounding breast tissue.

Mucinous Carcinoma (Colloid) [10]

Mucinous carcinoma is a rare type of invasive breast cancer that is formed when cancer cells within your breast produce mucous. This mucous contains breast cancer cells that are easily distinguished from normal cells under a microscope. Together, the mucous and cancer cells form a jelly-like tumor. Most mucinous carcinomas of the breast are estrogen-receptor positive and HER2/neu negative.

Cribriform Carcinoma of the Breast [11]

In invasive cribriform carcinoma, the cancer cells invade the stroma in nest like formations between the ducts and lobules. Within the tumor, there are distinctive holes in between the cancer cells, making it look something like Swiss cheese.

Papillary Carcinoma of the Breast [12]

An invasive papillary carcinoma usually has a well-defined border and is made up of small, finger-like projections.

Metaplastic Sarcomatoid Breast Carcinoma [13]

Metaplastic sarcomatoid breast carcinoma is a rare form of breast cancer in which there is a mixture of malignant mesenchymal and epithelial elements. Metaplastic breast carcinoma is an aggressive cancer, and tends to present at a more advanced stage and has a high propensity for local recurrence.

Inflammatory Breast Cancer [14]

Inflammatory Breast Cancer is an aggressive and fast growing breast cancer in which cancer cells infiltrate the skin and lymph vessels of the breast. It often produces no distinct tumor or lump that can be felt and isolated within the breast. But when the lymph vessels become blocked by the breast cancer cells, symptoms begin to appear.

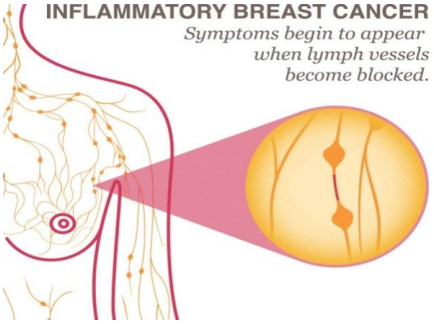


Fig. 4: Inflammatory Breast Cancer.

Early inflammatory breast cancer symptoms like persistent itching and the appearance of a rash or small irritation similar to an insect bite. The breast typically becomes red, swollen, and warm. The skin may appear pitted like an orange peel, and nipple changes such as inversion, flattening, or dimpling may occur.

Ductal Carcinoma in Situ (DCIS) [15]

DCIS is a non-invasive cancer where abnormal cells have been found in the lining of the breast milk duct. The atypical cells have not spread outside of the ducts into the surrounding breast tissue. The earliest stages of cancers are called “carcinoma in situ.” Carcinoma means “cancer” and in situ means “in the original place.”

Triple Negative Breast Cancer [16]

A diagnosis of triple negative breast cancer means that the three most common types of receptors known to fuel most breast cancer growth–estrogen, progesterone, and the HER-2/neu gene–are not present in the cancer tumor.

Metastatic Breast Cancer [17]

Metastatic breast cancer is also classified as Stage 4 breast cancer and it has spread to other parts of the body. This usually includes the lungs, liver, bones or brain.

Medullary Carcinoma [18]

The tumor usually shows up on a mammogram, but does not always feel like a lump. At times, it feels like a spongy change of breast tissue. It’s name from its color, which is close to the color of brain tissue medulla. It starts in milk ducts, with large cancer cells that look very different from healthy cells. These medullary carcinoma cells tend to form a clear boundary between the tumor and healthy tissue right next to them.

Paget Disease of the Breast or nipple [19]

This type of cancer affecting the skin of the nipple and often the areola, which is the darker circle of skin around the nipple. Most people with Paget disease evident on the nipple also have one or more tumors inside the same breast; generally either Ductal carcinoma in situ or invasive breast cancer.

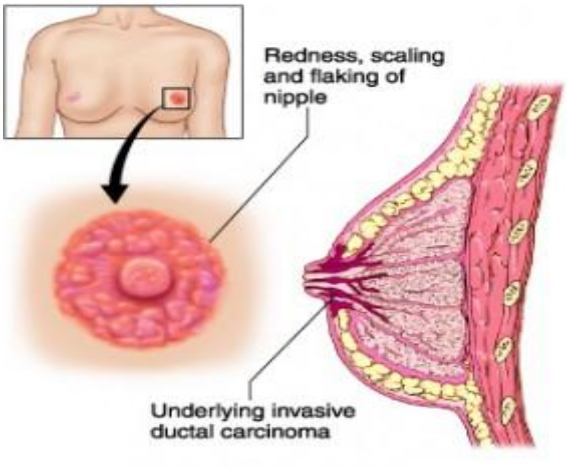


Fig. 5: Paget Disease of the Breast.

Breast cancer during pregnancy [20]

Breast cancer during pregnancy is rare and women who are diagnosed with it at this time often feel very isolated. Finding out that they have breast cancer can cause many different emotions, including shock, fear, depression and anxiety.

Breast Cancer Causes [21, 22, 23]

Age and gender

Gender is the biggest risk because breast cancer occurs mostly in women. Age is another critical factor. Breast cancer may occur at

any age, though the risk of breast cancer increases with age. The average woman at 30 years of age has one chance in 280 of developing breast cancer in the next 10 years. This chance increases to one in 70 for a woman 40 years of age, and to one in 40 at 50 years of age. A 60-year-old woman has a one in 30 chance of developing breast cancer in the next 10 years.

Genetic Causes

Family history has long been known to be a risk factor for breast cancer. Both maternal and paternal relatives are important. The risk is highest if the affected relative developed breast cancer at a young age, had cancer in both breasts. First-degree relatives (Mother, sister, and daughter) are most important in estimating risk. Several second-degree relatives (grandmother, aunt) with breast cancer may also increase risk. Breast cancer in a male increases the risk for all his close female relatives. There is great interest in genes linked to breast cancer. About 5%-10% of breast cancers are believed to be hereditary, as a result of mutations, or changes, in certain genes that are passed along in families.*BRCA1* and *BRCA2* are abnormal genes that, when inherited, markedly increase the risk of breast cancer to a lifetime risk estimated between 40%-85%.Women who have the *BRCA1* gene tend to develop breast cancer at an early age.

Hormonal Causes

Hormonal influences play a role in the development of breast cancer. Women who start their periods at an early age (12 or younger) or experience a late menopause (55 or older) have a slightly higher risk of developing breast cancer. Conversely, being older at the time of the first menstrual period and early menopause tend to protect one from breast cancer. Having a child before 30 years of age may provide some protection, and having no children may increase the risk for developing breast cancer. Using oral contraceptive pills means that a woman has a slightly increased risk of breast cancer than women who have never used them.

Lifestyle and Dietary Causes

Breast cancer seems to occur more frequently in countries with high dietary intake of fat, and being overweight or obese is a known risk factor for breast cancer, particularly in post menopausal women.

The use of alcohol is also an established risk factor for the development of breast cancer. The risk increases with the amount of alcohol consumed. Women who consume two to five alcoholic beverages per day have a risk about one and a half times that of non-drinkers for the development of breast cancer. Studies are also showing that regular exercise may reduce a woman's risk of developing breast cancer.

Environmental Causes

Radiation treatment increases the likelihood of developing breast cancer but only after a long delay.

The signs and symptoms of breast cancer include [24]

A lump in the breast or underarm that persists after menstrual cycle. This is often the first apparent symptom of breast cancer. Lumps associated with breast cancer are usually painless, although some may cause a prickly sensation. Lumps are usually visible on a mammogram long before they can be seen or felt.

- Swelling in the armpit.
- Pain or tenderness in the breast. Although lumps are usually painless, pain or tenderness can be a sign of breast cancer.
- A noticeable flattening or indentation on the breast, which may indicate a tumor that cannot be seen or felt.
- Any change in the size, contour, texture, or temperature of the breast. A reddish, pitted surface like the skin of an orange could be a sign of advanced breast cancer.
- A change in the nipple, such as a nipple retraction, dimpling, itching, a burning sensation, or ulceration. A scaly rash of the nipple is symptomatic of Paget's disease, which may be associated with an underlying breast cancer.
- Unusual discharge from the nipple that may be clear, bloody, or another color. It's usually caused by benign conditions.

Diagnosis [25, 26, 27]

Medical history and physical exam

Breasts were thoroughly examined for any lumps or suspicious areas and to feel their texture, size, and relationship to the skin and chest muscles. Any changes in the nipples or the skin of breasts will be noted. The lymph nodes in armpit and above collarbones may be palpated, because enlargement or firmness of these lymph nodes might indicate spread of breast cancer.

Imaging tests used to evaluate breast disease

Imaging tests use x-rays, magnetic fields, sound waves, or radioactive substances to create pictures of the inside of body.

Diagnostic mammograms

A mammogram is an x-ray of the breast. Screening mammograms are used to look for breast disease in women who have no signs or symptoms of a breast problem. Screening mammograms usually take 2 views (x-ray pictures taken from different angles) of each breast.

A diagnostic mammogram can show:

- That the abnormality is not worrisome at all. In these cases the woman can usually return to having routine yearly mammograms.
- That a lesion has a high likelihood of being benign. In these cases, it is common to ask the woman to come back sooner than usual for her next mammogram, usually in 4 to 6 months.
- That the lesion is more suspicious, and a biopsy is needed to tell if it is cancer.

Magnetic resonance imaging (MRI) of the breast

MRI can be used along with mammograms for screening women who have a high risk of developing breast cancer, or it can be used to better examine suspicious areas found by a mammogram.

Breast ultrasound

Breast ultrasound is used to target a specific area of concern found on the mammogram. Ultrasound helps distinguish between cysts and solid masses and sometimes can help tell the difference between benign and cancerous tumors, ultrasound may be most helpful in women with very dense breasts.

Ductogram

This test, also called a galactogram, sometimes helps determine the cause of nipple discharge. In this test a very thin plastic tube is placed into the opening of the duct in the nipple that the discharge is coming from. A small amount of contrast medium is injected, which outlines the shape of the duct on an x-ray image and shows if there is a mass inside the duct.

Nipple discharge exam

If women have nipple discharge, some of the fluid may be collected and looked at under a microscope to see if any cancer cells are in it. Most nipple discharges or secretions are not cancer. In general, if the secretion appears milky or clear green, cancer is very unlikely. If the discharge is red or red-brown, suggesting that it contains blood, it might possibly be caused by cancer, although an injury, infection, or benign tumors are more likely causes.

Biopsy

A biopsy is done when mammograms, other imaging tests, or the physical exam finds a breast change that is possibly cancer.

During a biopsy, a sample of the suspicious area is removed to be looked at under a microscope. There are several types of biopsies, such as fine needle aspiration biopsy, core (large needle) biopsy, and surgical biopsy. Each has its pros and cons.

Fine needle aspiration biopsy (FNA)

In a FNA biopsy, the doctor uses a very thin, hollow needle attached to a syringe to aspirate a small amount of tissue from a suspicious area, which is then looked at under a microscope.

If the area to be biopsied can be felt, the needle can be guided into the area of the breast change while the doctor is feeling it.

If the lump can't be felt easily, the doctor might use ultrasound to watch the needle on a screen as it moves toward and into the mass.

Once the needle is in place, fluid is drawn out. If the fluid is clear, the lump is probably a benign cyst. Bloody or cloudy fluid can mean either a benign cyst or, very rarely, a cancer. If the lump is solid, small tissue fragments are drawn out. A pathologist will look at the biopsy tissue or fluid under a microscope to determine if it is cancerous.

Core needle biopsy

A core biopsy uses a larger needle to sample breast changes felt by the doctor or pinpointed by ultrasound or mammogram.

The needle used in core biopsies is larger than the one used in FNA. It removes a small cylinder (core) of tissue (about 1/16- to 1/8-inch in diameter and ½-inch long) from a breast abnormality.

Vacuum-assisted biopsies

For these procedures the skin is numbed and a small incision (about ¼ inch) is made. A hollow probe is inserted through the incision into the abnormal area of breast tissue. The probe can be guided into place using x-rays or ultrasound. A cylinder of tissue is then suctioned in through a hole in the side of the probe, and a rotating knife within the probe cuts the tissue sample from the rest of the breast. Several samples can be taken from the same incision.

Surgical (open) biopsy

Usually, breast cancer can be diagnosed using needle biopsy. Rarely, surgery is needed to remove all or part of the lump for microscopic examination. This is referred to as a *surgical biopsy* or an *open biopsy*. Most often, the surgeon removes the entire mass or abnormal area as well as a surrounding margin of normal-appearing breast tissue. This is called an *excisional biopsy.* If the mass is too large to be removed easily, only part of it may be removed. This is called an *incisional biopsy*.

Lymph node biopsy

Even if no lymph nodes are enlarged, the lymph nodes under the arm are usually checked for cancer spread when the breast tumor is removed at surgery. This is done with a sentinel lymph node biopsy and/or an axillary lymph node dissection

Breast cancer grade

Invasive Ductal Carcinoma

Histologic tumor grade is based on the arrangement of the cells in relation to each other: whether they form tubules; how closely they resemble normal breast cells, and how many of the cancer cells are in the process of dividing (mitotic count).

- Grade 1 (well differentiated) cancers have relatively normal-looking cells that do not appear to be growing rapidly and are arranged in small tubules.
- Grade 2 (moderately differentiated) cancers have features between grades 1 and 3.
- Grade 3 (poorly differentiated) cancers, the highest grade, lack normal features and tend to grow and spread more aggressively.

Ductal carcinoma in situ (DCIS)

DCIS is also graded, but the grade is based only on how abnormal the cancer cells appear. The presence of necrosis is also noted. The term *comedocarcinoma* is often used to describe DCIS with necrosis. If a breast duct is filled with a plug of dead and dying cells, the term *comedonecrosis* may be used. The terms *comedocarcinoma* and *comedonecrosis* are linked to a higher grade of DCIS.

Estrogen receptor (ER) and progesterone receptor (PR) status

An important step in evaluating a breast cancer is to test a portion of the cancer removed during the biopsy (or surgery) to see if they have estrogen and progesterone receptors. Cancer cells may contain neither, one, or both of these receptors. Breast cancers that have estrogen receptors are often referred to as *ER-positive* (or ER+) cancers, while those containing progesterone receptors are called *PR-positive* (or PR+) cancers. If either type of receptor is present, the cancer is said to be *hormone receptor-positive*.

HER2/neu status

About 1 of 5 breast cancers have too much of a growth-promoting protein called HER2/neu (often just shortened to HER2). The *HER2/neu* gene instructs the cells to make this protein. Tumors with increased levels of HER2/neu are referred to as *HER2-positive*.

Women with HER2-positive breast cancers have too many copies of the *HER2/neu gene*, resulting in greater than normal amounts of the HER2/neu protein.

Tests of ploidy and cell proliferation rate

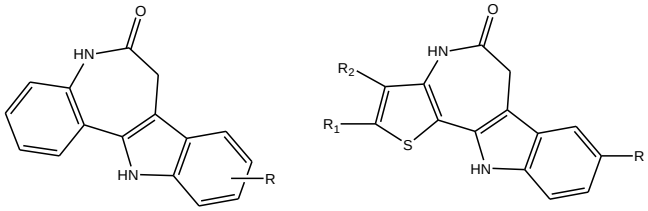
The ploidy of cancer cells refers to the amount of DNA they contain. If there's a normal amount of DNA in the cells, they are said to be *diploid*. If the amount is abnormal, then the cells are described as *aneuploid.*

Positron emission tomography (PET) scan

For a PET scan, glucose (a form of sugar) that contains a radioactive atom is injected into the bloodstream. Because cancer cells grow rapidly, they absorb large amounts of the radioactive sugar. After about an hour, a special camera is used to create a picture of areas of radioactivity in the body.

MOLECULES UNDER CLINICAL TRIAL FOR THE TREATMENT OF BREAST CANCER

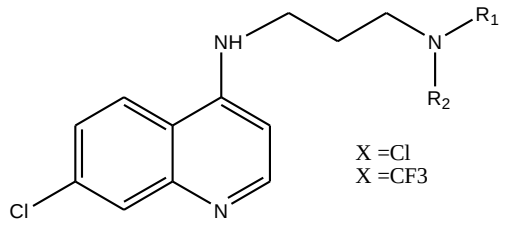
Brault L. et al. have reported “New thiophene analogues of kenpaullone: synthesis and biological evaluation in breast cancer cells” [28].



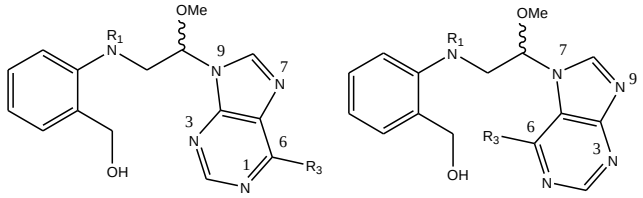
1. General structure of paullones.

Compounds	R	R_1	R_2
3a	Br	H	H
3b	H	tBu	H
3c	Br	tBu	H
3d	H	Ph	CH_3
3e	Br	Ph	CH_3

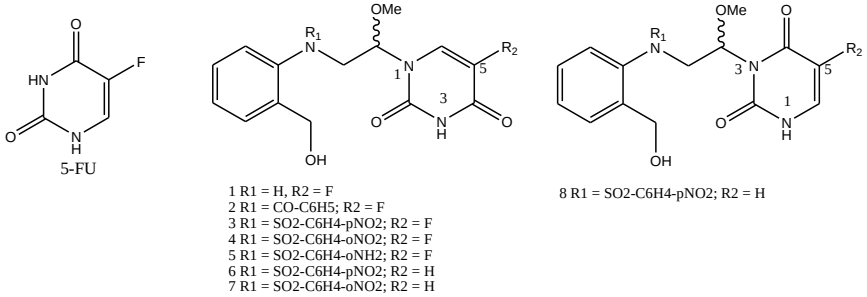
Solomon V.R. et al. have reported “Chloroquine analogs with anti-breast cancer property” [29].

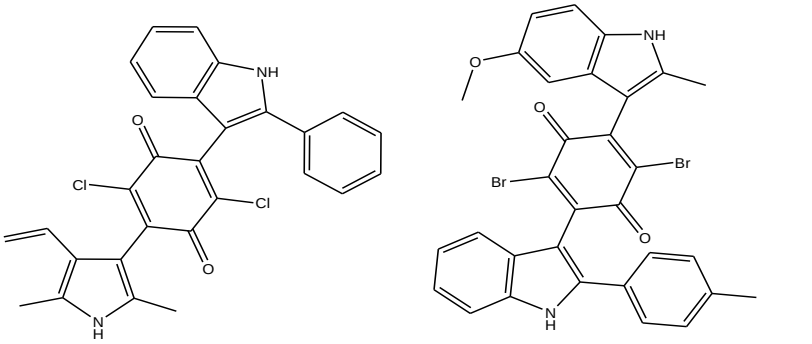


Caba O. et al. have reported “The selective cytotoxic activity in breast cancer cells by an anthranilic alcohol derived acyclic 5-flurouracil, N-acetal is mediated by endoplasmic reticulum stress induced apoptosis” [30].

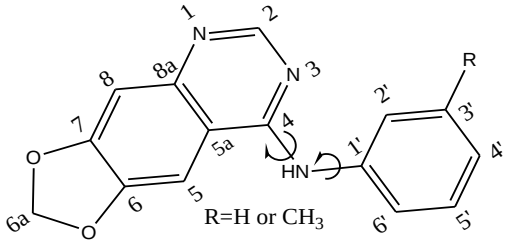


Li X. et al. has reported “anti-breast cancer activity of new indolyl quinone derivatives” [31].

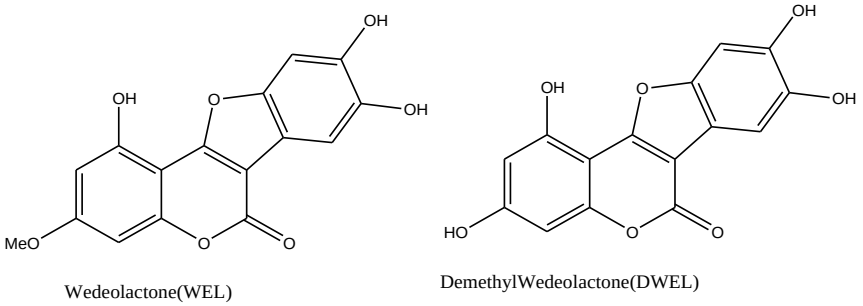




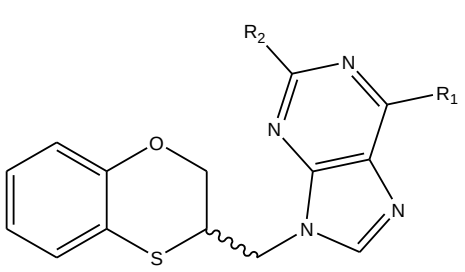
Oliveira A. et al. have reported “New substituted 4-arylaminoquinazolines as potent inhibitors of breast tumor celllines” [32].



Lee Y. J. et al. have reported “Demethylwedelo lactone derivatives inhibit invasive growth in vitro and lung metastasis of MDA-MB-231 breast cancer cells in nude mice” [33].

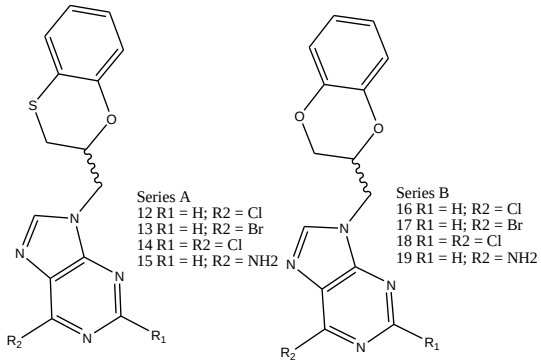


Conejo-García A. et al. have reported “anticancer activity of (RS)-9-(2,3-dihydro-1,4-benzoxaheteroin-2-ylmethyl)-9H” [34].



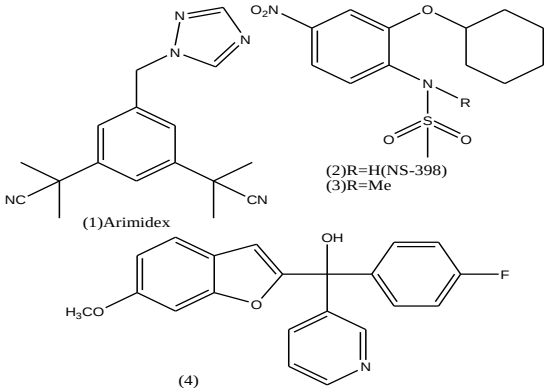
1 R_1 = H, R_2 = Cl
2 R_1 = H; R_2 = Br
3 R_1 = R_2 = Cl
4 R_1 = H; R_2 = SMe
5 R_1 = H; R_2 = OPh
6 R_1 = H; R_2 = SPh
7 R_1 = H; R_2 = NHPh
8 R_1 = H; R_2 = $OCH_2CH=CH_2$
9 R_1 = H; R_2 = OCH_2Ph
10 R_1 = H; R_2 = SCH_2Ph
11 R_1 = H; R_2 = $OCH_2C_6H_{11}$

Fig. 1. Series of substituted (RS)-9-(2,3-dihydro-1,4-benzoxathiin-3-ylmethyl)-9Hpurine derivatives 1e11 [10]



Substituted (RS)-9-(2,3-dihydro-1,4-benzoxathiin-2-ylmethyl)-9H-purines 12e15 (series A) and (RS)-9-(2,3-dihydro-1,4-benzodioxin-2-ylmethyl)-9H-purines 16e19 (series B).

Westwell A. D. have reported “New aromatase inhibitors with potential in breast cancer treatment” [35].



Han Y. et al. have reported “modulation of breast cancer resistance protein (bcrp/abcg2) by non-basic chalcone analogues” [36].

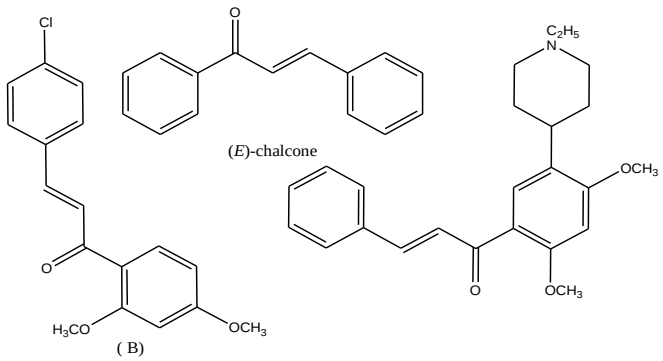
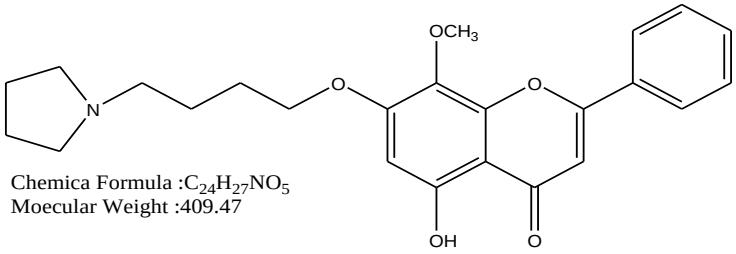


Fig. 1 – Structures of (A) the basic chalcone 1-[5-(1-ethylpiperidin-4-yl)-2,4-dimethoxyphenyl]-3-phenylprop-2-en-1-one, and (B) chalcone 6.

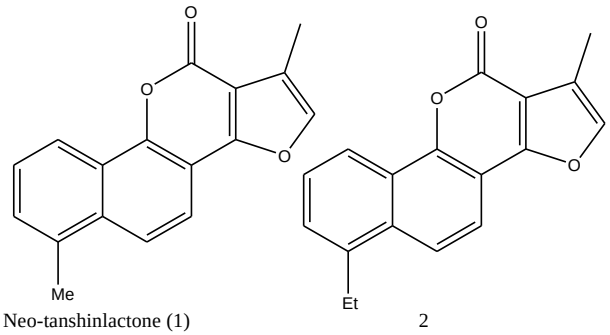
Li L. et al. have reported “Inhibitory effects of GL-V9 on the invasion of human breast carcinoma cells by down regulating the expression and activity of matrix metalloproteinase-2/9” [37].



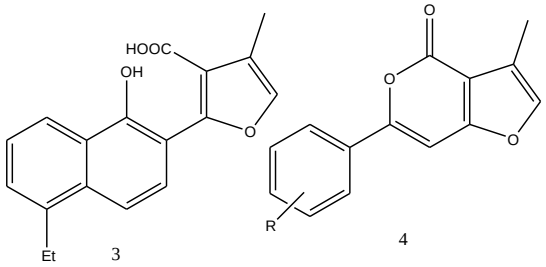
Chemica Formula :$C_{24}H_{27}NO_5$
Moecular Weight :409.47

5-hydroxy-8-methoxy-2-phenyl-7-(4-(pyrrolidin-1-yl)butoxy)-4*H*-chromen-4-one

Dong.Y. have reported "Antitumor agents 270. Novel substituted 6-phenyl-4H-furo[3,2-c]pyran-4-one derivatives as potent and highly selective anti-breast cancer agents" [38].



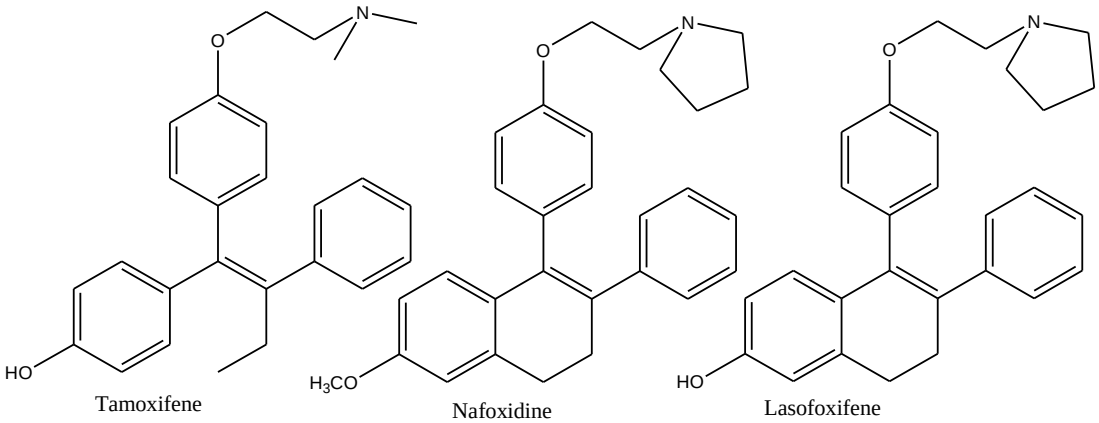
Neo-tanshinlactone (1) 2



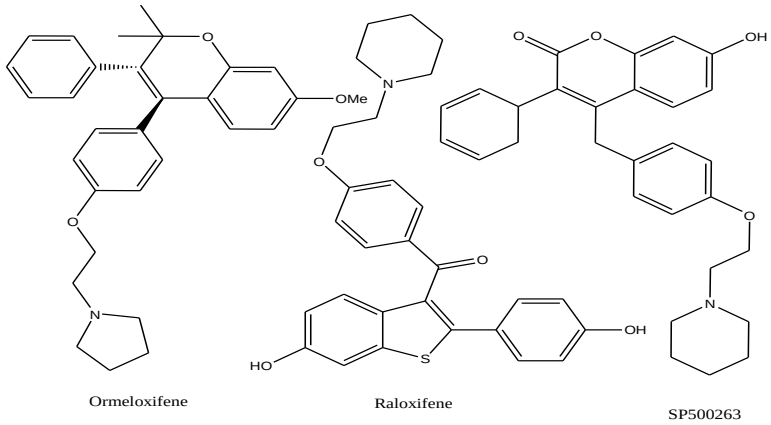
3 4

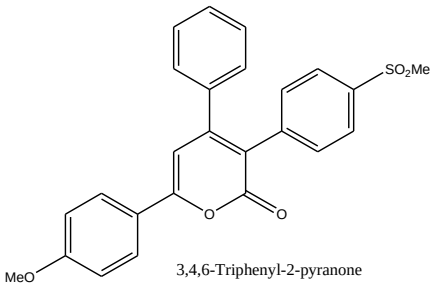
Structures of neo-tanshinlactone (1), a first generation neo-tanshinlactone analog 2, a second generation optimized analog 3, and a newly designed scaffold 4.

Shankar R. et al. have reported" Synthesis and biological evaluation of 3,4,6-triaryl-2-pyranones as a potential new class of anti-breast cancer agents" [39].



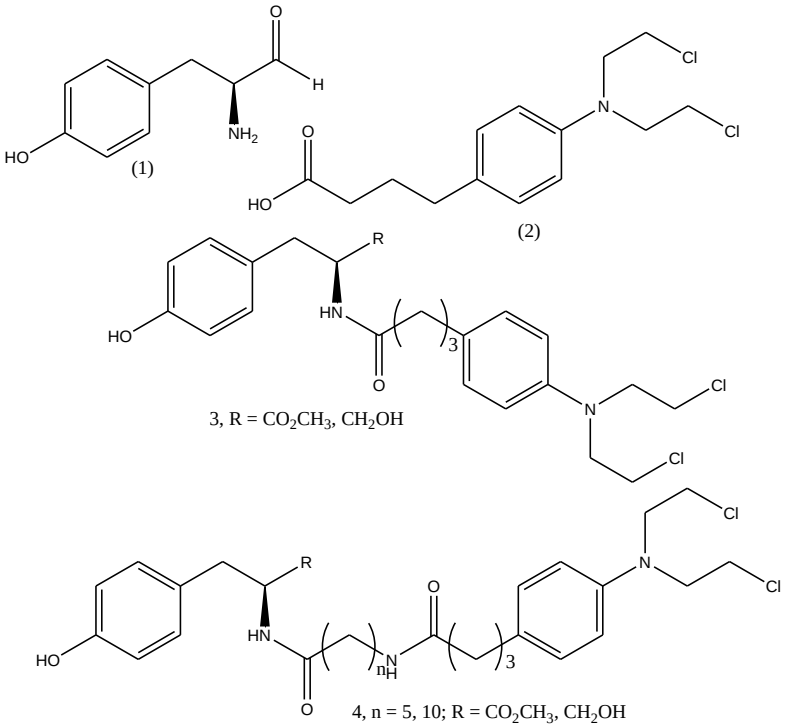
Tamoxifene Nafoxidine Lasofoxifene





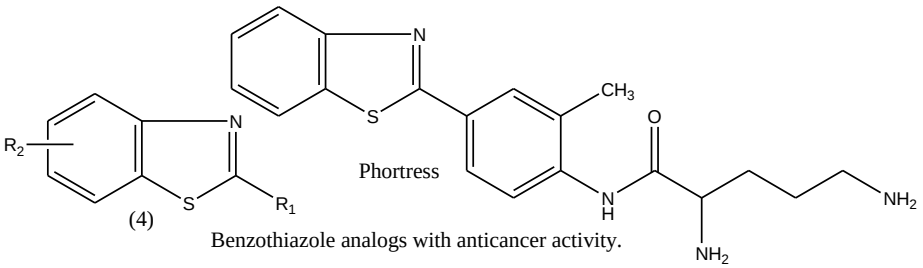
Structure of non steroidal estrogen antagonist

Descoteaux C. et al. have reported “Synthesis of D- and L-tyrosine-chlorambucil analogs active against breast cancer cell lines” [40].

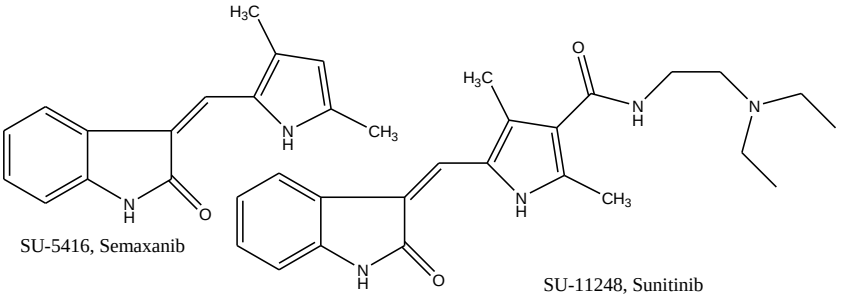


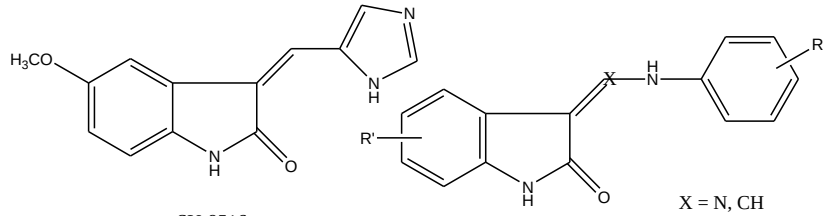
Structures of L-tyrosine (1), chlorambucil (2) and tyrosine derivatives 3 and 4.

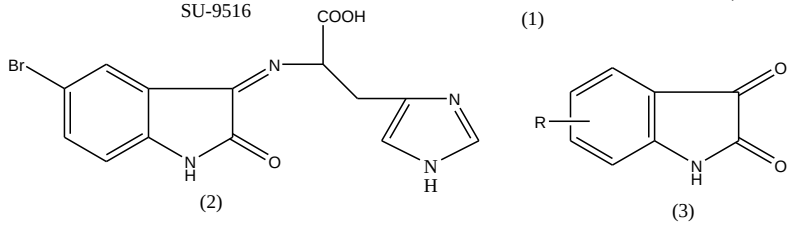
Solomon V. et al. have reported “Hybrid pharmacophore design and synthesis of isatin–benzothiazole analogs for their anti-breast cancer activity” [41].



Benzothiazole analogs with anticancer activity.

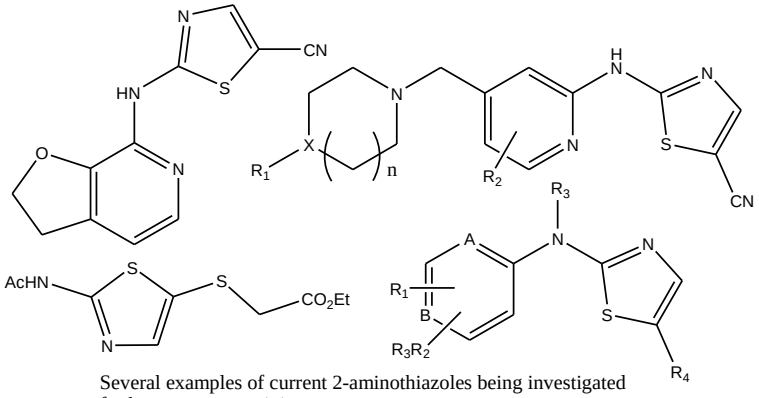






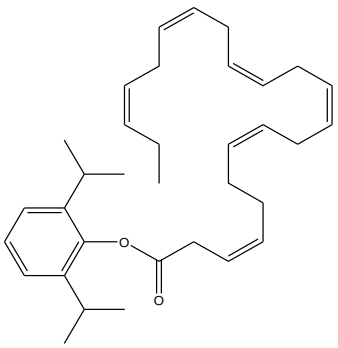
Isatin analogs with anticancer activity.

Gorczynski M. et al. have reported “Synthesis and evaluation of substituted 4-aryloxy- and4-arylsulfanyl-phenyl-2-aminothiazoles as inhibitors ofhuman breast cancer cell proliferation” [42].

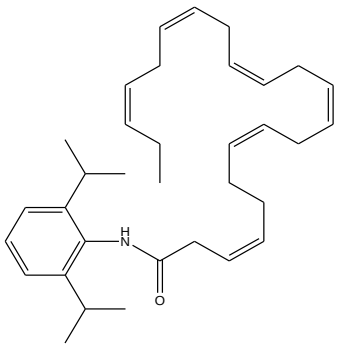


Several examples of current 2-aminothiazoles being investigated for breast cancer activity.
Figure

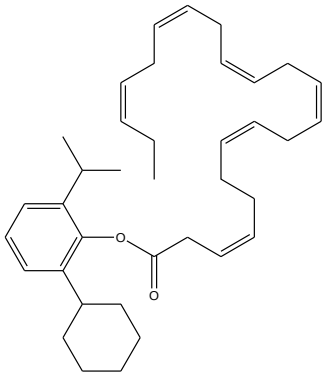
Harvey K. et al. have reported “anticancer properties of 2,6-diisopropylphenol–docosahexaenoate and analogues in breast cancer cells” [43].



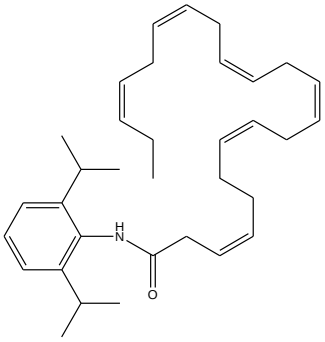
2,6-Diisopropylphenyldocosahexaenoate
(PP-DHA)



2,6-Diisopropylphenyldocosahexaenoamide
(DIPA-DHA)

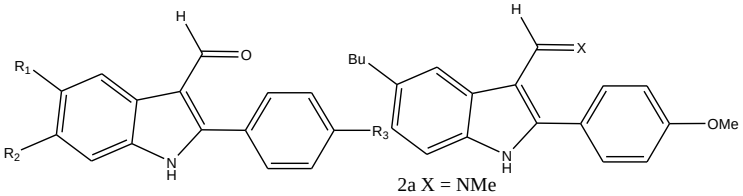


2-Cyclohexylphenyldocosahexaenoate
(CHP-DHA)



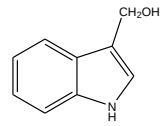
Phenyldocosahexaenoamide
(A-DHA)

Pojarova M. et al. have reported "[(2-Phenylindol-3-yl)methylene]propane dinitriles inhibit the growth of breast cancer cells by cell cycle arrest in G2/M phase and apoptosis" [44].

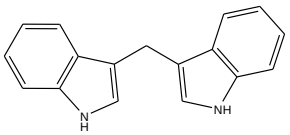


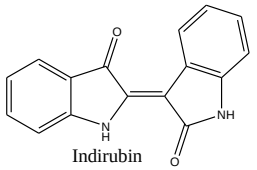
R_1 = H, alkyl, F, OCH_3
R_2 = H, Cl, F, OCH_3
R_3 = H, alkyl, OCH_3, CF_3

2a X = NMe
2b X = NOH

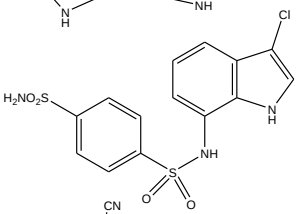


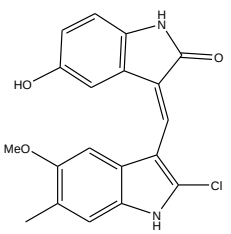
Indole-3-carbinol

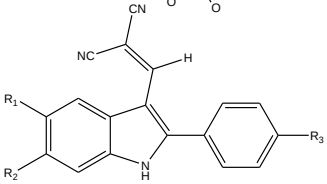




Indirubin



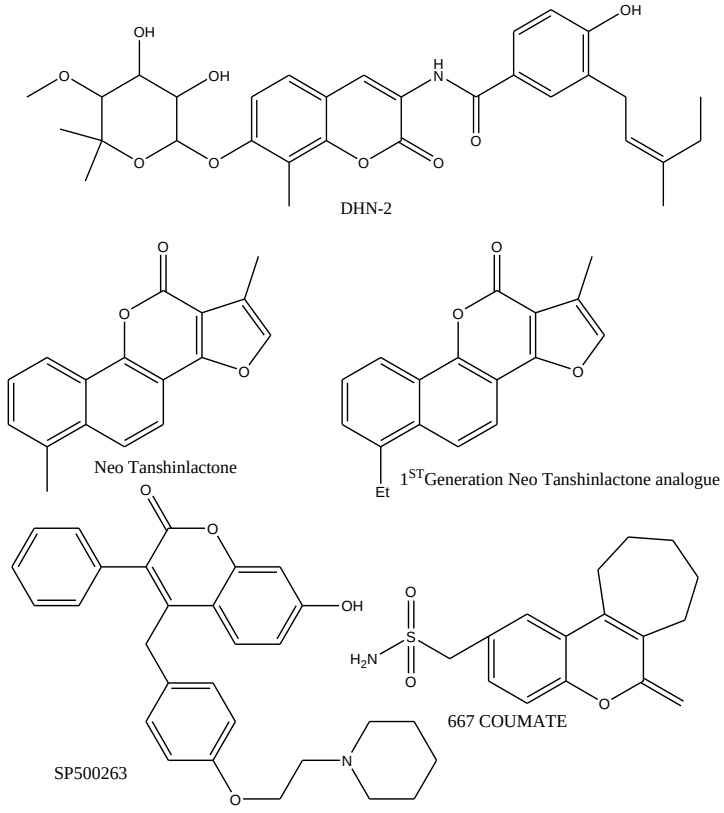




R1 = H, alkyl, F, OCH3
R2 = H, Cl, F, OCH3
R3 = H, alkyl, OCH3, CF3

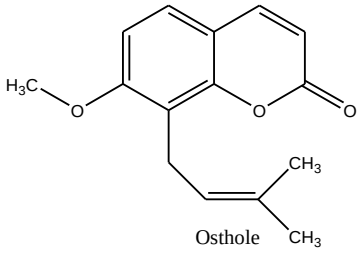
Example for indole derived agents that inhibit cell cycle progression through different mechanism

Sashidhara K.V. et al. have reported “Neo-tanshinlactone inspired synthesis, in vitro evaluation of novel substituted benzocoumarin derivatives as potent anti-breast cancer agents” [45].

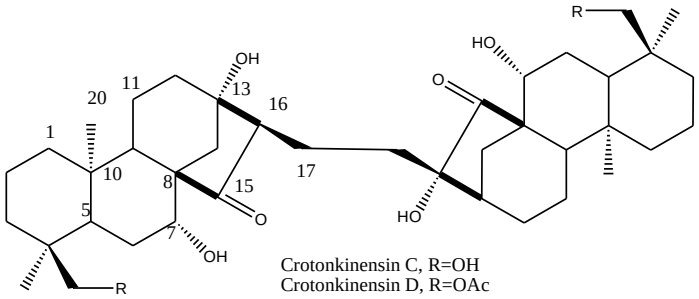


Examples of some potent coumarins having anti breast cancer activity

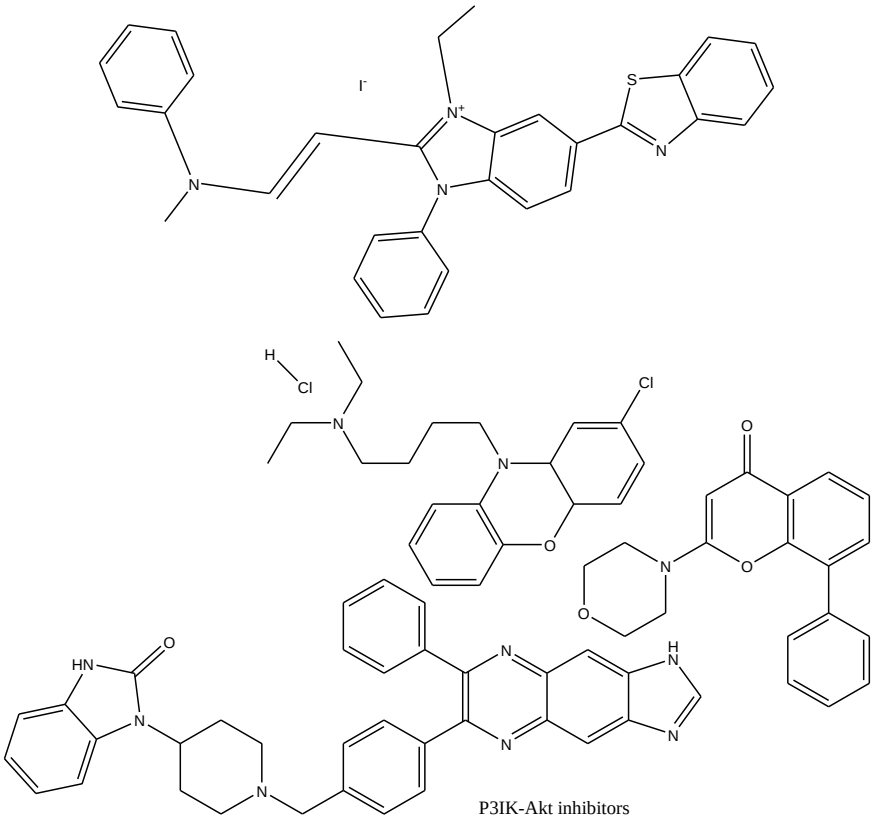
You L. et al. have reported “Discovery of novel osthole derivatives as potential anti-breast cancer treatment” [46].



Thuong P. T. et al. have reported “Symmetric dimmers of ent-kaurane diterpenoids with cytotoxic activity from Crotontonkinensis” [47].



Hua C. et al. have reported “A 4-aminoquinoline derivative that markedly sensitizes tumor cell killing by Akt inhibitors with a minimum cytotoxicity to non-cancer cells” [48].



P3IK-Akt inhibitors

REFERENCES

1. Boyle P, Howell A. The globalisation of breast cancer. Breast Cancer Research 2010; 12(4):57.
2. Ferlay J. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int. J. Cancer. 2010; 127(12):2893-2917.
3. Tanis P. J. Anatomy and physiology of lymphatic drainage of the breast from the perspective of sentinel node biopsy. J Am Coll Surg 2001; 192(3):399-409.
4. Webb P. M. Family history of breast cancer, age and benign breast disease. International Journal of Cancer 2002; 100(3):375-378.
5. Santen RJ, Mansel R. Benign breast disorders. N Engl J Med. 2005; 353:275-285.
6. Guray M, Sahin AA. Benign breast diseases: Classification, diagnosis, and management. Oncologist. 2006; 11:435-449.
7. Lewis JT, Hartmann LC, Vierkant RA. An analysis of breast cancer risk in women with single, multiple, and atypical papilloma. Am J Surg Pathol. 2006; 30:665-672.
8. Myron A. Infiltrating ductal carcinoma of the breast associated with primary breast lymphoma. Journal of Cancer 2011; 2:186-192.
9. Rakha EA. Tubular carcinoma of the breast: further evidence to support its excellent prognosis. J Clin Oncol 2010; 28(1):99-104.
10. Laucirica R. Performance characteristics of mucinous (colloid) carcinoma of the breast in fine-needle aspirates. Arch Pathol Lab Med. 2011; 135:1533–1538.
11. Page DL. Invasive cribriform carcinoma of the breast. Histopatology 1983; 7(4):525-536.
12. Pal S. Papillary carcinoma of the breast: An Overview. Breast Cancer Res Treat. 2010 ; 122(3):637–645.
13. Kurian KM, Al-Nafussi A. Sarcomatoid/metaplastic carcinoma of the breast: a clinicopathological study of 12 cases. Histopathology 2002; 40:58-64
14. Fred V. Inflammatory carcinoma of the breast. Cancer 1978; 41:1595-1605.
15. Burstein H. J. Ductal Carcinoma in Situ of the Breast. The New England journal of medicine 2004; 350:1430-1441.
16. William D. Tripal negative breast cancer. The New England journal of medicine 2010; 363:1938-1948.
17. Stevanovic A. Metastatic breast cancer. Reprinted from Australian Family Physician 2006; 35(5):309-312.
18. Baum M., Edwards M. H. Medullary carcinoma of breast. British Medical Journal 1970; 29(3):521.
19. Nance F. C. Paget disease of breast. Ann Surg. 1970; 171(6):864–874.
20. Roman Rouzier R. Management of breast cancers during pregnancy. Breast Cancer and Pregnancy 2008: 1-28.
21. Lichtenstein Environmental and heritable factors in the causation of cancer: analyses of cohorts of twins from Sweden, Denmark, and Finland. N Engl J Med 2000; 343(2):78-85.
22. Schoenfeld et. al. Electromagnetic fields and breast cancer on Long Island: a case-control study. Am J Epidemiol 2003; 158(1): 47-58.
23. Rudel P. Environmental exposures and mammary gland development: state of the science, public health implications, and research recommendations. Environ Health Perspect 2011; 119(8):1053-1061.
24. Bower J. Behavioral Symptoms in Patients with Breast Cancer and Survivors. Journal of Clinical Oncology 2008; 26(5):768-777.
25. Katajal V. Castiglio M. Primary breast cancer: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol. 2009; 20(4):10-14.
26. Elizabeth A. Breast cancer: A multidisciplinary approach to diagnosis & Management, 1st edn. Taghian AG. Demos medical publishing, 2010: 68-81.
27. Walter M. Recent advance in breast imaging, mammography & computer aided diagnosis of breast cancer, 1st edn. Suri J., Rangaggan R. The international society for optical engineering, 2006; 51-60.
28. Laurent B. New thiophene analogues of kenpaullone : synthesis and biological evaluation in breast cancer cells. European Journal of Medicinal Chemistry 2005; 40:757–763.
29. Solomon V. Design and synthesis of chloroquine analogs with anti-breast cancer property. European Journal of Medicinal Chemistry 2010; 45:3916-3923.
30. Octavio C. The selective cytotoxic activity in breast cancer cells by an anthranilic alcohol derived acyclic 5-fluorouracil O, N-acetal is mediated by endoplasmic reticulum stress-

induced apoptosis. European Journal of Medicinal Chemistry 2012; 50:376-382.
31. Xue Li. Synthesis and anti-breast cancer activity of new indolyl quinone derivatives. European Journal of Medicinal Chemistry 2012; 54:42-48.
32. Andre O. New substituted 4-arylaminoquinazolines as potent inhibitors of breast tumor cell lines: In vitro and docking experiments. European Journal of Medicinal Chemistry 2010; 45:4339-4342.
33. Yean-Jang L. Demethylwedelolactone derivatives inhibit invasive growth in vitro and lung metastasis of MDA-MB-231 breast cancer cells in nude mice. European Journal of Medicinal Chemistry 2012; 56:361-367.
34. Ana CG. Synthesis and anticancer activity of (RS)-9-(2,3-dihydro-1,4-benzoxaheteroin-2-ylmethyl)-9H-purines. European Journal of Medicinal Chemistry. 2011; 46: 3795-3801.
35. Andrew W. New aromatase inhibitor with potential in breat cancer treatment. Drug Discovery Today 2006; 11:21-22.
36. Yi H. Modulation of breast cancer resistance protein (BCRP/ABCG2) by non-basic chalcone analogues. European journal of pharmaceutical sciences 2008; 35:30–41.
37. Liwen L. Inhibitory effects of GL-V9 on the invasion of human breast carcinoma cells by down regulating the expression and activity of matrix metalloproteinase-2/9. European Journal of Pharmaceutical Sciences 2011; 43:393–399.
38. Yizhou D. Novel substituted 6-phenyl-4H-furo[3,2-c]pyran-4-one derivatives as potent and highly selective anti-breast cancer agents. Bio. org. Med. Chem. 2010; 18: 803–808.
39. Shankar R. et al. Synthesis and biological evaluation of 3,4,6-triaryl-2-pyranones as a potential new class of anti-breast cancer agents. Bio. org. Med. Chem. 2009; 17:3847–3856.
40. Caroline D. Synthesis of D- and L-tyrosine-chlorambucil analogs active against breast cancer cell lines. Bio. org. Med. Chem. Lett. 2010; 20:7388–7392.
41. SolomonV. Hybrid pharmacophore design and synthesis of isatin–benzothiazole analogsfor their anti-breast cancer activity. Bio. org. Med. Chem. 2009; 17:7585–7592.
42. Michael G. Synthesis and evaluation of substituted 4-aryloxy-and4-arylsulfanyl-phenyl-2-aminothiazoles as inhibitors of human breast cancer cell proliferation. Bio. org. Med. Chem. 2004; 12:1029–1036.
43. Kevin H. Characterization of anticancer properties of 2,6-diisopropylphenol–docosahexaenoate and analogues in breast cancer cells. Bio. org. Med. Chem. 2010; 18:1866–1874.
44. Michaela P. [(2-Phenylindol-3-yl) methylene] propane dinitriles inhibit the growth of breast cancer cells by cell cycle arrest in G2/M phase and apoptosis. Bio. org. Med. Chem. 2007; 15:7368–7379.
45. Koneni SV. Neo-tanshinlactone inspired synthesis, in vitro evaluation of novel substituted benzocoumarin derivatives as potent anti-breast cancer agents. Bio. org. Med. Chem. Lett. 2010; 20:7127–7131.
46. Lisha Y. Discovery of novel osthole derivatives as potential anti-breast cancer treatment. Bio. org. Med. Chem. Lett. 2010; 20:7426–7428.
47. Thien TP. Symmetric dimers of ent-kaurane diterpenoids with cytotoxic activity from Croton tonkinensis. Bio. org. Med. Chem. Lett. 2012; 22:1122–1124.
48. Changkun H. A 4-aminoquinoline derivative that markedly sensitizes tumor cell killing by Akt inhibitors with a minimum cytotoxicity to non-cancer cells. European Journal of Medicinal Chemistry. 2010; 45:705–709.